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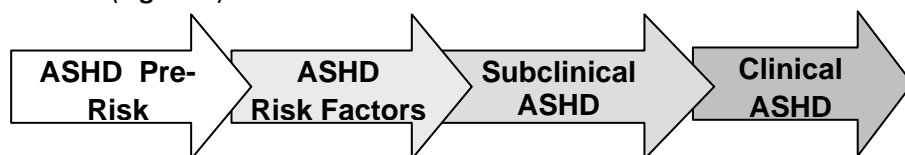
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<b>14. ABSTRACT</b>  This contract supports the installation and use of a research-dedicated 3 Tesla (3T) imaging system to measure the size, strength, and function of the heart as well as to quantify the atherosclerotic burden in the aorta and carotid arteries in a multi-ethnic, population based cohort (the Dallas Heart Study-2). It supports accelerated parallel imaging of the heart, abdominal aorta, and carotids, and brain and reduces the time required for imaging each subject. The detailed imaging data obtained on each participant will be integrated with classical risk factors, biomarkers, and genetic markers to produce individualized prescriptions for prevention of heart disease. The development of such prescriptions could be translated into clinical practice to reduce death and disability from atherosclerotic heart disease. To date, 1808 (with the 3T MRI covered by this grant) DHS-2 participants have undergone imaging of the brain, carotids, aorta, and heart, including measuring cardiac volumes, ventricular wall thickness and ejection fraction. A analysis of the MRI images for left ventricular function/mass, diastolic function, aortic atherosclerosis, carotid atherosclerosis, and brain volumes is in progress.				
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## I. Introduction

This contract supports the installation and use of a research-dedicated 3 Tesla (3T) magnetic resonance imaging (MRI) system to evaluate the heart and vascular system as proposed in the Dallas Heart Study-2 (DHS-2). The overall goal of the DHS-2 is to integrate detailed imaging of atherosclerosis in the aorta, carotids, and coronaries with classical risk factors, biomarkers, and genetic markers to produce individualized prescriptions for prevention of heart disease (***Prescriptions for Prevention***). In order to accomplish this goal, the Dallas Heart Study (DHS) was transformed from a cross-sectional health survey into a longitudinal cohort study. Nine years ago, we performed a detailed characterization of each participant in the DHS, which included state-of-the-art imaging of the heart and aorta using MRI and imaging of the coronary arteries using electron beam computer tomography (EBCT). Two years ago, we invited the original participants back to repeat the phenotyping and capture interval changes in the size and function of the heart and in the development and progression of atherosclerosis in the aorta and the coronary arteries. We have also added imaging studies of the brain and the carotids to the MRI protocol. Our objective is to pinpoint factors that contribute to the progression of disease in individuals: 1) from health to ASHD risk; 2) from having ASHD risk factors to developing sub-clinical ASHD; and 3) from sub-clinical ASHD to developing symptomatic ASHD (**Figure 1**).



**Figure 1:** Targeted points for prevention.

The 3T MRI supported by this contract is used to measure the size, strength, and function of the heart as well as to quantify the atherosclerotic burden in the aorta and carotid arteries. It supports accelerated parallel imaging of the heart, abdominal aorta, carotids and brain and reduces the time required for imaging each subject. The detailed imaging data obtained on each participant will be used to identify new factors contributing to the development and progression of heart disease.

## II. Scientific Progress

### A. 3T MRI Installation and Testing

The Philips Achieva 3.0T MRI system was installed on September 1, 2007 and was accepted for clinical use on September 28, 2007. The first DHS-2 participant was imaged on October 18, 2007. Image quality was assessed using standard phantoms and the system met performance criteria as specified by the American College of Radiology. Since the 3T System was installed, the software has been updated to version 2.5.3 to facilitate the use of new multichannel coils. These include a 16-channel torso coil for abdominal imaging and a 32-channel cardiac coil. The combination of new coils, software, and additional receiver channels allows us to reduce the time required for cardiac and aortic imaging. In addition, a special purpose carotid imaging coil was obtained from the University of Washington to quantify the amount of carotid atherosclerosis.

A physiologic monitoring system to facilitate the rapid scanning of DHS-2 participants was purchased and installed on September 29, 2007. We have two highly trained MRI technicians who scan our participants. The MRI system is integrated into the campus information systems, allowing the technologists to obtain work lists and easily transfer the recorded images for later analysis. To date, 1865 studies (1808 with the DOD 3T Magnet) have been performed. DHS-2 participants have undergone imaging of the brain, carotids, aorta, and heart, including measuring cardiac volumes, ventricular wall thickness and ejection

fraction. The studies take 1.5 hours and we plan to continue imaging participants through the end of December.

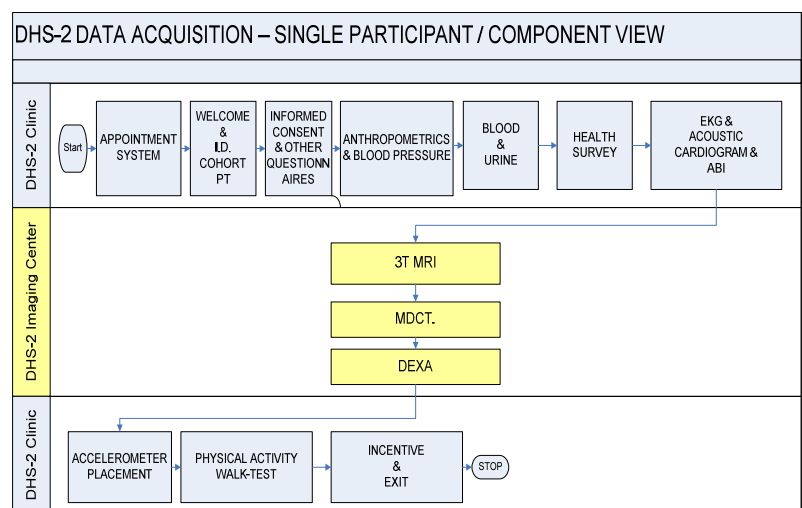
To facilitate analysis, we purchased and implemented software from Diagnosoft to assess systolic and diastolic function using HARP (harmonic phase) analysis of the tagged myocardial images. Dr. Nael Osman (Johns Hopkins), the developer of the software, visited Dallas, trained the DHS-2 investigators in this technique, and validated our acquisition and analysis protocols. The analysis of the MRI images for left ventricular function/mass, diastolic function, aortic atherosclerosis, carotid atherosclerosis, and brain volumes is in progress.

## **B. Determine interval change in cardiovascular risk factor profiles and ASHD in the Dallas Heart Study.**

**CLINIC VISIT:** The DHS clinic is located on the ground floor of UT Southwestern University Hospital-St. Paul with direct access to a dedicated parking lot. The clinic is located on the same level as the DHS-2 Imaging Center, which contains the 3T MRI, DEXA scanner and MDCT scanner. An overview of a single participant's clinic visit is provided in **Fig. 2**. The duration of the visit is 6-7 hours and lunch is provided.

The following 4 items take 90-120 minutes to complete:

- Informed consent
- Dallas-Ft. Worth Hospital Council Consent: This consent allows us to obtain records of hospitalizations in the Dallas-Fort Worth area. A total of 77% of the Visit 2/3 participants have signed the DFWHC consent (with 22 refusals, 325 dead, incarcerated or withdrawn, and 459 are pending).
- Medication history: Participants are instructed to bring medications with them. The name and dosage of each medication is recorded by clinic staff on the clinic data form. The data are then entered into the database.



**Fig. 2.** Schematic of study participant visit to the DHS clinic.

- Interval ASHD event questionnaire: Information regarding any cardiovascular event is obtained and recorded. Permission is obtained to get pertinent medical records.
- Survey: A web-based health survey is administered using direct computer response entry. Questions regarding socioeconomic status, family history, medical history, interval changes in health status, menopausal status and mental status are included. Survey instruments to assess the amount and intensity of exercise (MESA Physical Activity Questionnaire) and the severity of depressive symptoms (Quick Inventory of Depressive Symptomatology 16) are also used. Data from the survey are transferred and backed up directly to the DHS Database. The data are cleaned and verified prior to entry into a 'locked' version of the DHS-2 database. Interval quality assessments are performed to ensure that the data are captured accurately.
- Cognitive testing: all participants receive the Montreal Cognitive Assessment (MoCA), a validated instrument designed to detect cognitive impairment.

### **C. Determine the interval development and progression of coronary and abdominal aortic atherosclerosis**

As of August 25, 2009, 2909 participants have obtained imaging studies. These studies have generated over 2.8 million images.

Our goal in DHS-2 is to integrate detailed imaging of atherosclerosis in the aorta, carotids and coronary arteries with classical risk factors, biomarkers and genetic markers to develop an individual Prescription for Prevention.

**CAC progression:** In DHS-2, we are using MDCT rather than EBCT to measure coronary calcium (CAC). Images using this newer imaging modality are compared to baseline EBCT measures by adjusting both scan results to standardized scores using a calibration phantom as previously described.

**Incidence of coronary calcium:** Preliminary analyses of 698 subjects with paired scans from DHS-1 to DHS-2 were performed using these attenuation corrected scores. In this preliminary dataset with a mean scanning interval of 6.5 ( $\pm 0.6$ ) years, the prevalence of CAC was 25% in DHS-1 and increased to 35% in DHS-2 (**Fig. 3**). Of the 525 subjects without CAC ( $\leq 10$ ) in DHS-1, 15% developed incident CAC resulting in annual incidence rate of 2.3%. This estimate is consistent with observed values ( $\sim 2.5\%$  per year) for subjects with a mean age of 45 years seen in the MESA study.<sup>1</sup>

**Progression of coronary calcium:** In this same cohort of 698 subjects, 22% of the cohort increased CAC score category, 1% decreased category, and 77% had no change in category (**Table 1**). The mean annual % change in CAC score of the 173 subjects with CAC in DHS-1 was  $31 \pm 42\%$ , which is also consistent with values reported in other studies (30-40% per year).<sup>2-4</sup>

We are also quantifying the absolute progression in Agatston score in each of the major coronary arteries (**Figure 4**).

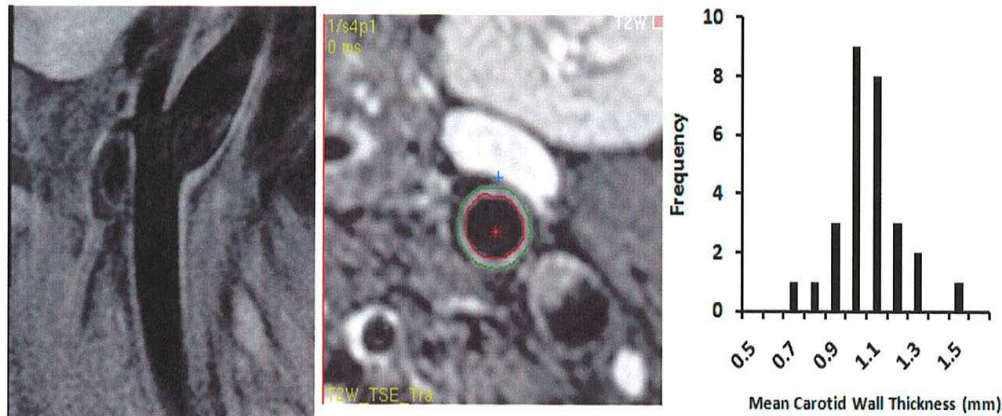
**Table 1.** Preliminary analyses of CAC progression from DHS-1 to DHS-2. CAC score categories presented in Agaston units. Values above and to the right of diagonal gray boxes indicate subjects with increasing CAC scores.

DHS1	DHS2				Total
	0-10	10-100	100-400	> 400	
0-10	446	64	12	3	525
10-100	6	51	44	6	107
100-400	0	1	20	26	47
> 400	0	0	1	18	19
Total	452	116	77	53	698

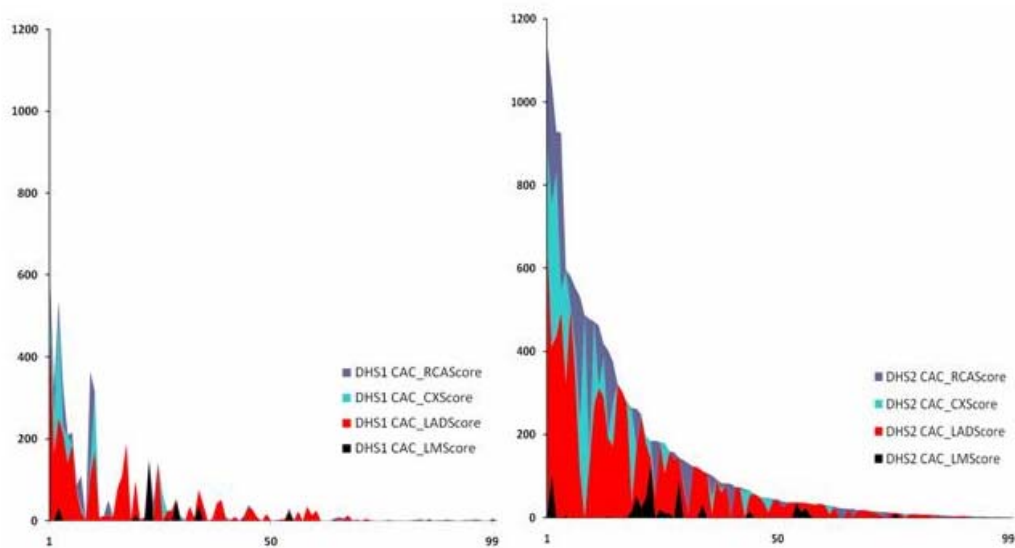
**Abdominal aortic plaque (AAP) and aortic wall thickness (AWT) imaging by MRI-3T:** The studies performed in DHS-1 are being replicated using a 3.0 T MRI system using methods described in detail previously. Variables include: *AAP incidence and AAP progression*, as defined previously. A paper describing the validation of using 3T MR for evaluation of abdominal plaque and aortic wall thickness was published this year<sup>5</sup>. In addition, a paper describing a new method for the determination of aortic wall thickness was published and is being used in the DHS2 analysis \*(Rosero EB, et al., Journal of Magnetic Resonance Imaging 2009;29:576-582).

**Future directions and translation to clinical practice:** We will investigate the determinants of incident and progressive AAP. We will determine if the early presence or extent of AAP, or greater AWT, predicts the early appearance of CAC. If AAP or AWT provide an earlier (and reliable) marker of subclinical atherosclerosis, it would permit earlier identification of patients at risk using a method that does not require

radiation or contrast.



**Figure 3.** (Left) Sagittal black blood image obtained using the 8-channel coil developed at the U. of Washington. (Middle) Axial image through the left carotid with superimposed automatically detected borders used for wall thickness calculation. (Right) Preliminary carotid wall thickness analysis in 27 participants.

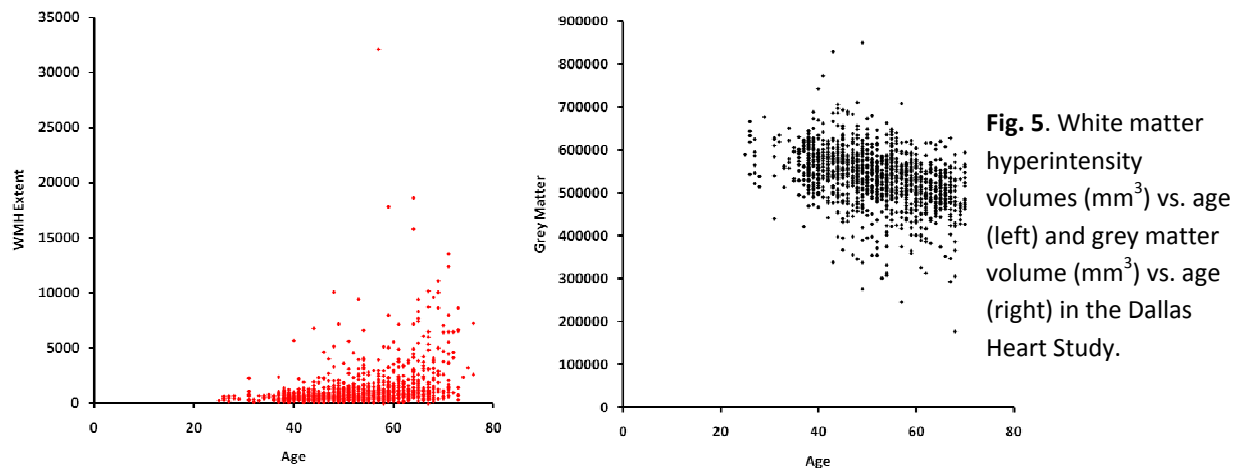


**Fig. 4.** Total CAC (Agatston score) and its distribution by vessel (LM, LAD, CX, RCA) for the top 100 scores in DHS-2 as of October 2008 (right) in comparison with the same participants in DHS-1 (left). Of note is the high frequency of CAC progression in the LAD. Also note the appearance of calcium in the RCA and Cx in participants with LAD CAC in DHS-1.

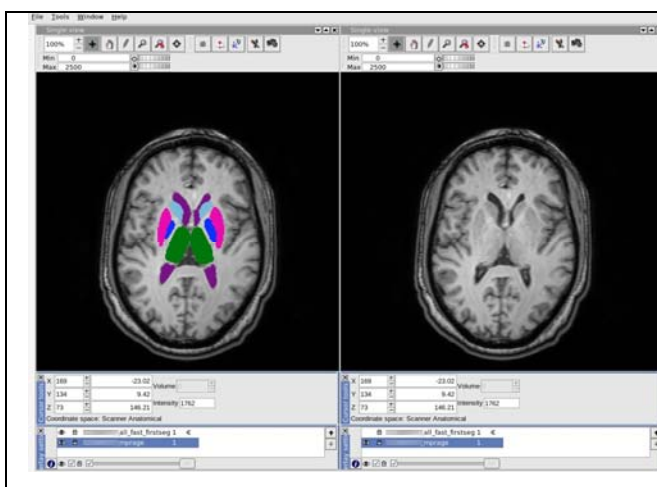
#### D. Quantify and characterize carotid artery atherosclerosis

The presence of carotid atherosclerosis predicts prevalent coronary atherosclerosis and ASHD events<sup>6-8</sup>. Adding carotid MRI to quantify and characterize carotid atherosclerosis in DHS-2 adds new information and establishes a baseline for future assessment of ASHD and carotid atherosclerosis risk and disease.

- Carotid MRI: Carotid images have been obtained in over 1800 participants. Working with Dr. Jarrett Berry, a new faculty member recruited from Northwestern University, the decision has been made to analyze the images using software from the University of Washington. This will permit comparison of the DHS-2 carotid data with other studies in which he is involved. This summer Dr. Berry trained on the software at the University of Washington and will begin analysis in September 2009.
- Brain MRI to assess brain volume and white matter hyperintensities: Brain images have now been obtained in 1820 participants. We continue to use the automated method described in the last progress report to calculate white matter volume, grey matter volume and white matter hyperintensity volume. We have also begun to perform automated segmentation of sub-cortical structures to address issues in regional brain atrophy. Update results are shown in (Figure 5).



**Fig. 5.** White matter hyperintensity volumes ( $\text{mm}^3$ ) vs. age (left) and grey matter volume ( $\text{mm}^3$ ) vs. age (right) in the Dallas Heart Study.



**Fig. 5a.** Sub- cortical segmentation. An axial image is shown with the automatically segmented ventricle (purple), thalamus (green), globus pallidus (dark blue), putamen (pink), and caudate (light blue). The original MRI image is on the right.

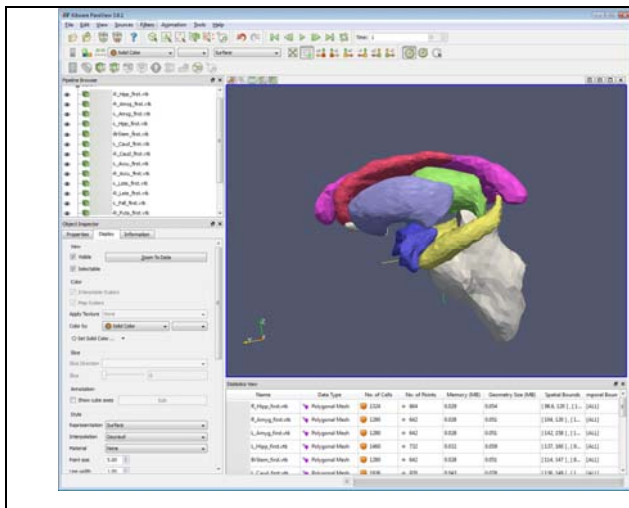


Fig. 5b. A 3D rendering of segmented subcortical structures in another participant. The brainstem (off white), hippocampus (yellow), amygdala (dark blue), putamen (grayish purple), thalamus (lime green), caudate (redish orange), and lateral ventricle (pink).

- **Future directions and translation to clinical practice:** Carotid MRI will allow us to further characterize the extent and distribution of atherosclerosis, complementing prior imaging with assessment in a third vascular bed. Carotids will be the only arteries in which we characterize the *composition* of atherosclerotic plaque. It serves as the basis for future progression studies and permits quantitative and qualitative association analyses with conventional ASHD risk factors, biomarkers and genetic variants. Clinical carotid evaluation using MRI is routine so new insights and techniques developed by this research could be rapidly disseminated into clinical practice. Brain MRI will allow evaluation of end-organ damage and correlation with measures of cognitive function.

### E. Determine interval change in heart size, shape and function.

By repeating cardiac MRI in DHS-2, we can determine changes in LV mass, volume, and systolic function after 7 years, allowing us to identify parameters at baseline that predict such adverse events as progressive cardiac hypertrophy, adverse ventricular remodeling, a fall in ejection fraction and heart failure.

In DHS-2 we have added myocardial tagging to permit state-of-the-art assessment of diastolic function.

- **Cardiac MRI:** Initial DHS-2 image analysis has been done in over 1544 participants for ventricular volumes and myocardial mass. Analysis of the corresponding DHS-1 images using the same software is underway to ensure that changes in software version and readers since DHS-1 have no effect.
- **Myocardial tagging:** Myocardial tagging has been done in over 1300 participants and initial image analysis using the HARP program from Johns Hopkins has been completed in

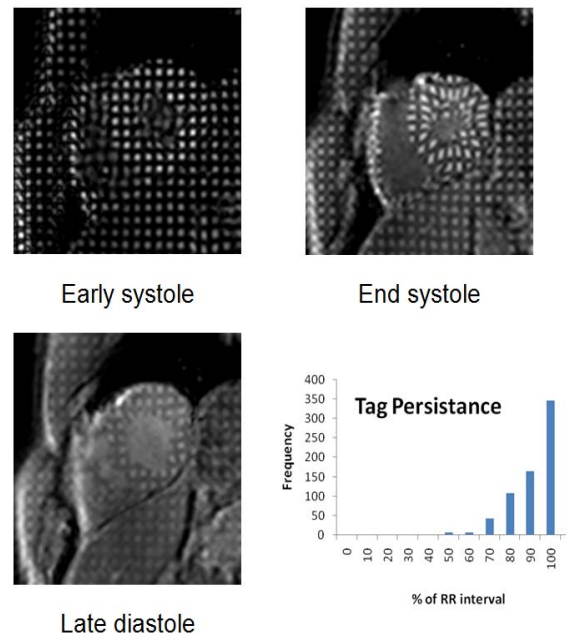
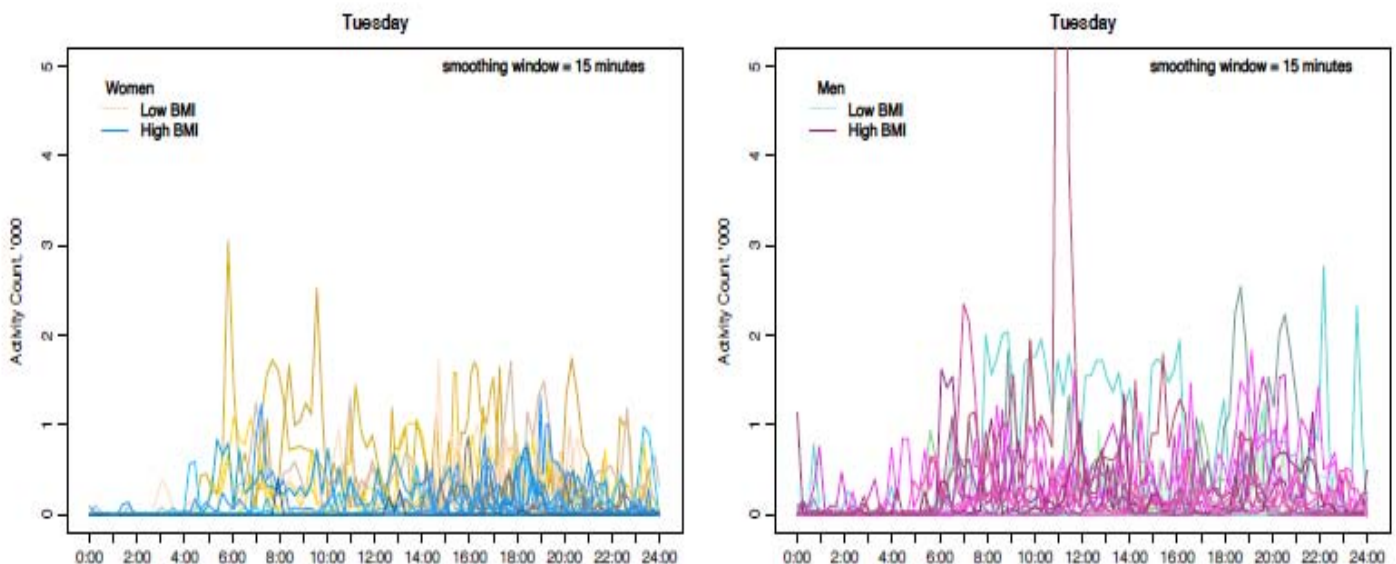


Fig. 6. Short axis, tagged MRI images obtained in early systole, end systole and late diastole showing tag persistence. The histogram in the right lower panel shows that the most participants have tags which persist late in the cycle which will permit analysis of diastolic function.

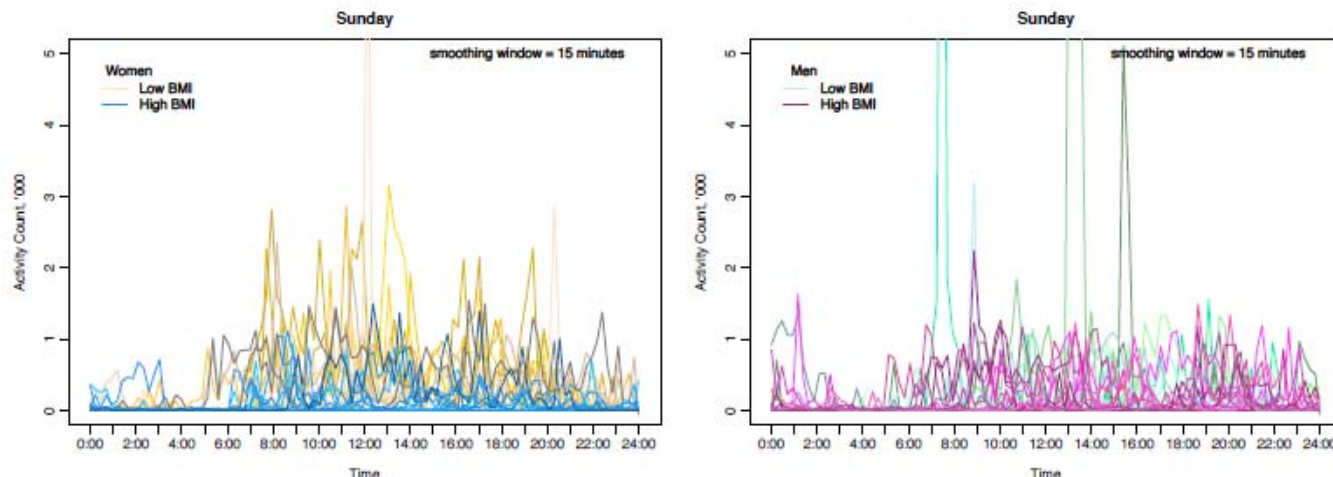
over 1232 participants. Image quality for the tagging studies has been very good with tag persistence well into diastole which will allow us to investigate early diastolic relaxation (**Figure 6**).

- Acoustic cardiogram: The Audicor Acoustic Cardiogram evaluates the electrical and the acoustical activities of the heart. Our pilot data using this technique is based on a study of 36 subjects with systolic heart failure. Six acoustic electrocardiographic readings were performed per subject to assess reproducibility. We found acceptable reproducibility of S3 (ICC [intraclass correlation coefficient] 0.71) and S4 (ICC 0.76) but the reproducibility of electromechanical activation time (EMAT) was better (0.81). EMAT represents the time from onset of QRS to the mitral component of S1, a reported measure of cardiac function. The mean (SD) EMAT was 126 (30) msec in this pilot study. Analysis of 2,300 subjects from DHS-2 found that the EMAT was 85 (15) msec less than that seen in patients with systolic heart failure. In preliminary analysis of 838 subjects in DHS-2 with a cardiac MRI, EMAT was weakly, but significantly, associated with ejection fraction ( $r = -0.08$ ,  $p = 0.03$ ) and LV mass ( $r = 0.1$ ,  $p = 0.002$ ). In similar preliminary analyses from DHS-2, S4 intensity was not associated with LV mass ( $p = 0.06$ ) but S3 was associated with LV end-diastolic volume ( $r = 0.1$ ,  $p = 0.006$ ) and inversely with concentricity ( $r = -0.15$ ,  $p < 0.001$ ). Further analyses of acoustic cardiographic parameters will clarify whether this technology has a role in screening for left ventricular structural and functional abnormalities in the general population.
- Physical fitness testing: A 4 minute treadmill exercise tolerance test (ETT) that measures heart rate changes during submaximal exercise is being performed on every participant. These values can be extrapolated to maximal oxygen uptake. Heart rates are measured at up to 4 speeds over 4 minutes.
- 8-day physical activity measurement using an accelerometer: The Actical activity monitor provides an objective, quantifiable measure of physical activity and energy expenditure. Sleep patterns and amount of sleep are also monitored. This will allow us to test if phenotypic differences in individuals are predicted by patterns of activity. Fig. 7 and 8 demonstrate differences in activity patterns between very obese and lean subjects for both men and women.



**Fig. 7.** Preliminary analysis of activity data. Activity counts averaged over 15 min intervals for a 24-h period during the week in very obese (BMI 50-60) (blue) and lean (BMI 20-21) (yellow) women (left) and very obese (BMI 45-65) (purple) and lean (BMI 20-22) (green) men (right).  $n = 12$  in each group. Note, men tend to be more active than women during the week. Very obese women and men are significantly less active than the corresponding nonobese women and men.

Note that activity is higher in lean compared to very obese individuals regardless of gender. Men are more active during the week (illustrated with data taken from a Tuesday) as shown on **Fig. 7**., whereas women tend to be more active on weekends, except for a few very active men (**Fig. 8**).



**Fig. 8.** Preliminary analysis of activity data from a weekend day (same individuals as show in **Fig. 7**). Activity counts averaged over 15 minute intervals for a 24-h period on Sunday in very obese (blue) and lean (yellow) women (left) and very obese (purple) and lean (green) men (right). Note, in contrast to during the week, women tend to be more active than men on the weekend, with a few exceptions of men who are very active.

#### CLINICAL REPORTS TO PARTICIPANT:

A report is provided to each DHS-2 participants of their clinic visit and includes:

- Brachial BP (mean of last 3 measurements)
- Lipid profile with interpretations
- Complete blood count, Chem 24, and results from urinalysis
- Percentage (%) of body fat and body mass index
- ECG (with clinically-relevant abnormalities reported)
- Coronary artery calcium score with interpretation
- LV hypertrophy (present/absent)
- LV ejection fraction with interpretation

#### COHORT FOLLOW-UP

In cohort follow-up, our major focus is on Visit 2 and Visit 3 (n=3557) participants from DHS-1, since these individuals are most important for participation in DHS-2 and have undergone blood sampling and imaging. The status of cohort follow-up for those participants is summarized in **Table 2**.

**Table 2.** Status of cohort follow-up amount DHS-1 participants who completed Visits 2 and 3 (n=3557).

Category	N	Percentage of V2/V3 Cohort
Follow-up	3116	88%
Deceased*	178 (up from 154)	4%
Incarcerated	37 (up from 23)	<1%
Withdrawn	136 (up from 113)	3%
Lost to follow-up	25 (up from 3)	<1%
Tracing	277 (up from 160)	4%
Other (inactive)	3 (up from 2)	<1%
Available for DHS-2	2901	82%

\* Includes National Death Index and DHS Call Center death reports.

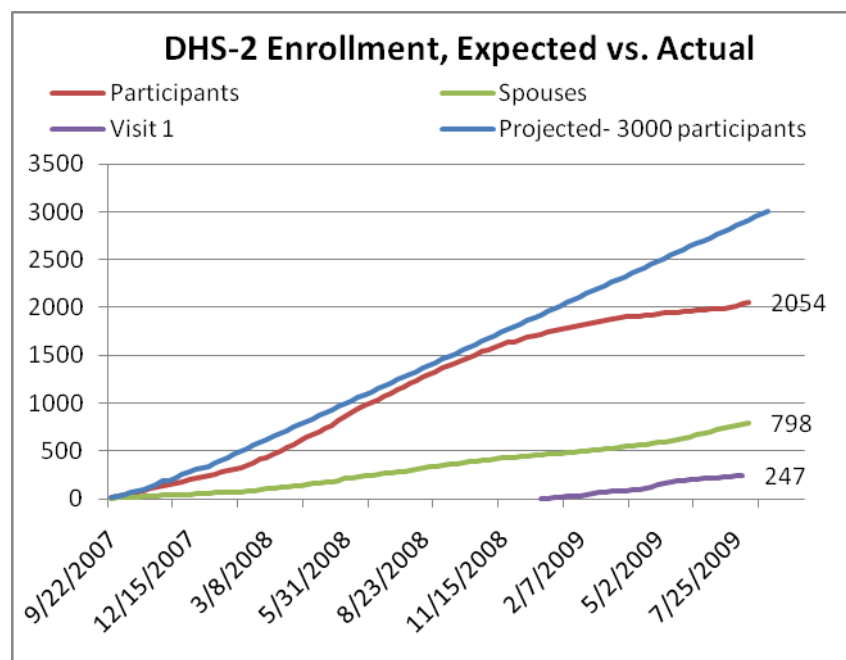
## DHS ENROLLMENT

Shown in **Figure 9** is the enrollment of DHS-2. Our goal has been to enroll a total of 3,000 subjects, although only 2000 participants from DHS-1 are required for us to address the Specific Aims of the project. Participation rates have fallen recently despite instituting multiple different strategies. To increase the number of participants we instituted the following strategies:

- In 1/09 we invited participants only completing DHS-1 visit 1 (at home survey) to come to the clinic.
- Initially, we invited only a spouse or significant other to accompany a participant; we have now extended the invitation to any family member.
- Family members now obtain the same studies as the participant (previously they did not receive imaging studies).
- Participation rates and no-show rates are closely monitored to project future participation levels. Reasons for refusal are recorded using standardized codes.
- We have visited the homes of the participants for whom we have addresses but no phone numbers.

In order to ensure that participation will not fall below the required power calculation we have:

- 1) Reviewed reasons for refusal.
- 2) Changed the hours of the clinic to include evenings.
- 3) Offered partial visits for participants who have concerns regarding a particular procedure.
- 4) Increased incentive package (added \$25 gift card to encourage returns to complete visit and increased total compensation from \$150 to \$250).
- 5) Augmented the sample with individuals from DHS-1 who completed Visit 1 (ages 30-65).



**Fig. 9.** Enrollment in DHS-2. A total of 2000 subjects are required to address the Specific Aims of our grant

**DATA SECURITY:** Access to the data is limited to the DCC staff. All data collected by the DHS are protected in accordance with applicable IRB, informed consent, and HIPAA regulations. Coded forms that do not include personal identifiers are used for data collection. Only tracking form(s) have the participant's name and address. Study records are in locked cabinets in a secured room. Only authorized study personnel have access to the data and codes. All computerized information is protected by access codes known only to the PI and designated DCC staff members. All staff are trained to maintain participant confidentiality, and no data are published with participant names.

The research and operational DHS databases are located in the UT Southwestern Data Center, which provides physical and electronic data protection and disaster recovery options. Data in the Data Center are periodically backed-up off-site in a different city, and the ability to restore the data has been confirmed. Release of data to investigators is made available through 'locked versions' of the database to provide a system of accountability. The DCC team monitors server storage utilization so that newly acquired information from DHS Cohort participants can be effectively stored and routinely backed up.

#### **F. Preventing the progression of LVH to heart failure.**

Here we are using a comprehensive, multi-pronged strategy to identify individuals in the general population who are at risk for developing LVH, those who have LVH or LV dysfunction, and those with LVH who are at risk of developing ASHD and heart failure. By improving our ability to detect and risk stratify LVH before the development of clinical symptoms, appropriate interventions may be implemented earlier in the disease process.

- Determine if a new classification of LV geometry predicts the development of coronary heart disease, systolic dysfunction, and clinical heart failure among those with obesity-related LVH

Obesity-related LVH is at epidemic levels in Dallas County, especially in ethnic minorities. A critical unanswered question is whether obesity-related LVH should be treated irrespective of BP. A total of 53% of women and 44% of men in the DHS with obesity-related LVH did not have hypertension. Although obesity is a risk factor for CHF, >80% of obese individuals in Framingham did not develop heart failure after 15 years<sup>9</sup>. Similarly, LVH has a low positive predictive value as a risk factor for ASHD<sup>10</sup>. Here we will test the following hypothesis:

**HYPOTHESIS:** *Individuals with obesity-related LVH and eccentric or concentric hypertrophy are at greater risk for development of ASHD, reduced LVEF and heart failure than individuals with proportional hypertrophy. Further refinements in the phenotype of obesity-related LVH may identify the subset of individuals at sufficient risk to merit intervention. We proposed a new classification scheme for LVH. Individuals are classified into four categories based on the ratios of LV mass to LV volume, and LV wall thickness (LVWT) to LV volume: concentric hypertrophy (↑LV mass/volume), eccentric hypertrophy (↓LVWT/volume), and "proportional" hypertrophy (neither increased LV mass/volume or reduced LVWT/volume).*

#### **Related findings/progress this year:**

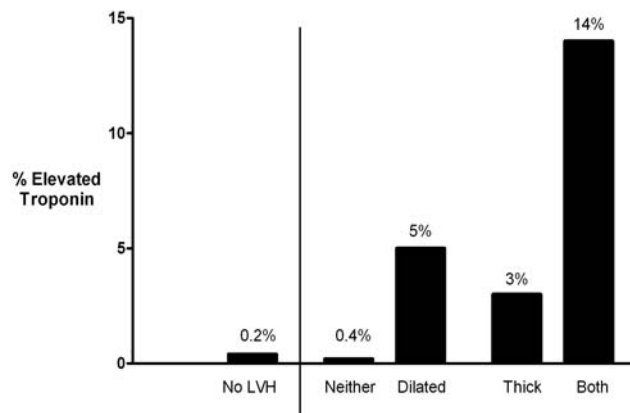
- New classification scheme for cardiac hypertrophy. We have revised our classification of LVH (increased LV mass/height<sup>2.7</sup>) into 4 profiles based on whether concentricity (LV mass/volume, a marker of concentric remodeling) or LV end-diastolic volume/BSA (a marker of chamber dilation) is increased. We have termed these patterns: thick-walled (increased concentricity); dilated (increased LVEDV/BSA); both thick-walled and dilated hypertrophy; or neither thick-walled or dilated hypertrophy. The numbers of participants in the DHS-1 in each of these classes are:

1) Thick-walled hypertrophy - 345

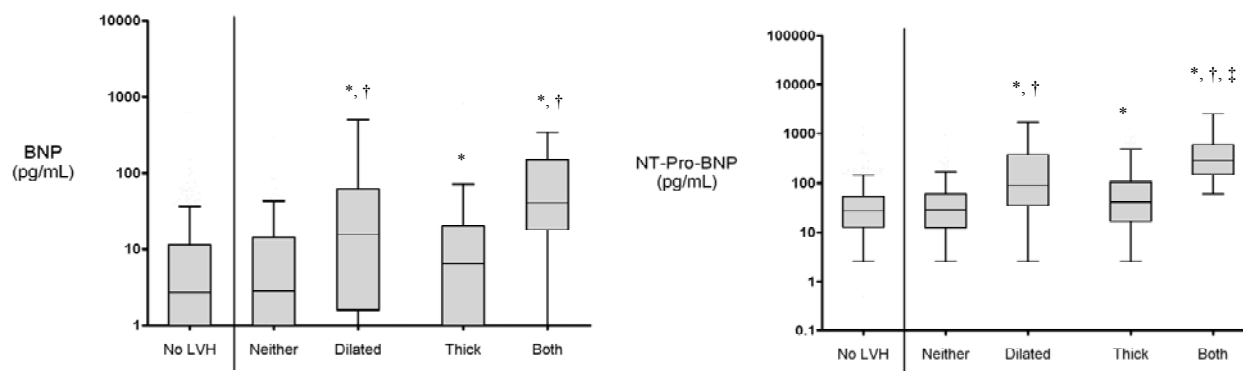
- 2) Dilated hypertrophy - 57
- 3) Thick-walled and dilated hypertrophy – 14
- 4) Not thick-walled or dilated hypertrophy - 479.

LVH that did not meet criteria for thick-walled or dilated hypertrophy appears to be a lower risk phenotype than LVH with thick-walled and/or dilated hypertrophy as measured by association with risk markers including Troponin T (Fig. 10) and natriuretic peptides (Fig. 11).

**Future directions and translation to clinical practice:** With the emerging epidemic of obesity, addressing the question of how to assess risk in patients with obesity-related increases in LV mass has clear public health implications, impacting over 20% of Whites, 50% of Blacks, and 40% of Hispanic women in Dallas County. The existence of high-risk patterns (e.g., concentric or eccentric hypertrophy) would warrant a clinical trial of preventive strategies in such individuals. Future questions we will address include: is eccentric remodeling a precursor to eccentric hypertrophy? Is concentric remodeling a precursor to concentric hypertrophy? What is the role of diastolic dysfunction in the transition from LVH to clinical heart failure?



**Fig. 10 Prevalence of elevated troponin T in subjects stratified by presence and type of LVH.** “Neither” represents subjects with increased LV mass (LVH) but without criteria for significant ventricular dilation or increased wall thickness. Dilated represents subjects with LVH and significant ventricular dilation; Thick represents subjects with LVH with significantly increased concentricity; and Both represents subjects with both ventricular dilation and increased concentricity.



**Fig. 11.** Plasma BNP and NT-pro-BNP Levels by presence and type of LVH. Median values, *line within the box*; Interquartile range, 25<sup>th</sup> and 75<sup>th</sup> percentiles, *lower and upper box margins*, respectively; 5<sup>th</sup> and 95<sup>th</sup> percentiles, *lower and upper ends of whiskers*, respectively. \*P<0.001 vs. Neither †P≤0.001 vs. Thick ‡P<0.05 vs. Dilated.

### **G. Beyond Framingham: more accurate predictors for the development and progression of ASHD.**

Prediction of ASHD could potentially be improved by three emerging modalities that are not included in the Framingham Risk Score: *direct imaging of atherosclerosis*, *biomarkers*, and *genetic markers*. In this Aim, we are developing methods to improve the prediction of ASHD risk in an individual using a combination of these modalities and established risk factors.

We are proceeding in a step-wise fashion to develop an individualized prescription to prevent ASHD, including CAC incidence, CAC progression and ultimately ASHD events. We will next determine if the morphological/compositional characteristics of atherosclerosis in multiple arterial beds (coronary, aorta and carotid), circulating biomarkers of inflammation, and DNA sequence variants associated with early symptomatic ASHD predict disease progression and clinical events in the DHS. We will develop an integrated risk prediction algorithm that includes the imaging modalities and markers that are most predictive of disease progression. Finally, we will validate and refine the algorithm developed in the DHS in the ARIC cohort.

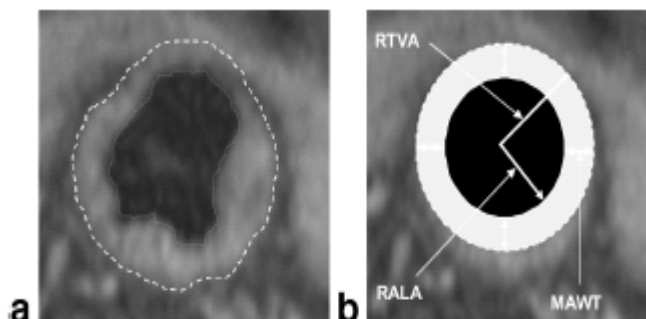
#### **H. To determine if atherosclerosis in the abdominal aorta and carotids predicts the incidence and progression of coronary artery calcification and coronary events.**

Direct imaging of atherosclerosis can provide three important indices of ASHD risk. An image taken at a single time-point quantitates *total atherosclerotic burden*, which is strongly correlated with symptomatic ASHD<sup>11,12</sup>. In addition, serial images taken over time can be used to directly assess the *progression of atherosclerosis* in an individual and provide incremental prognostic information<sup>13</sup>. Finally qualitative aspects of lesions such as *morphology and composition* may complement quantitative measures of atherosclerotic burden by revealing vulnerable plaques, thereby identifying vulnerable patients<sup>14</sup>.

**HYPOTHESIS**: *MRI measurements of atherosclerosis in the abdominal aorta and carotid arteries are independent predictors for the incidence and progression of CAC, and for incident CV events.*

As outlined in the original grant we will perform the following studies:

- Determine if abdominal aortic plaque (AAP) or aortic wall thickness (AWT) in DHS-1 is associated with the incidence, extent and progression of CAC, and if so, whether the association is modified by gender.
- Determine the level of concordance/discordance between incident AAP, AWT and CAC.
- Assess if AAP and AWT are associated with an increased risk for ASHD clinical events.
- Test for an association between quantitative and qualitative carotid artery wall measures by MRI and prevalent CAC and AAP.
- Test for an association between carotid artery wall measures and plaque composition types with the *progression* of CAC and AAP.



**Fig. 12.** Axial image of abdominal aorta with luminal and adventitial borders circumscribed (a). Method of calculated mean AWT (MAWT) involves determining the radius of the circle encompassing the total vessel areal (RTVA) and radius of a circle encompassing the luminal area (RALA) (b).

#### **Related findings/progress this year:**

- Completion of CAC, abdominal aortic atherosclerosis, and carotid artery imaging in 1260 subjects.
- Validation of an automated method to measure aortic wall thickness. The association between carotid intima-medial thickness and cardiovascular events highlights the importance of vessel wall thickening in the study of CHD. To determine risk associated with even earlier phases of atherogenesis, we derived a new phenotype from our abdominal aortic MRI measurements, aortic wall thickness (AWT), which we previously described. We have recently compared methods for quantifying AWT based on averaging multiple measurements of the aortic

radii measured using an automated method versus using a mathematical derivation of AWT by calculating the cross sectional areas<sup>15</sup> (**Figure 12**). Our results validated the approach using cross sectional areas and

suggests that it is more accurate than older methodology; this will be the method we use to quantify AWT in DHS-2.

**Future directions and translation to clinical practice:** These atherosclerosis imaging techniques have great promise for individualizing and improving upon cardiovascular risk prediction and will be incorporated into a risk prediction algorithm. We will identify subgroups who are more likely to have atherosclerotic disease, for which earlier scanning may be beneficial. We will also continue to accrue CV event data to determine the relationship of atherosclerosis progression to incident CV events.

#### **I. Determine the relationship between biomarkers and the development and progression of ASHD.**

Biomarkers that accurately predict the incidence and progression of ASHD complement direct imaging in two ways. First, biomarkers may be informative even before the development of ASHD, whereas direct imaging can only detect disease that is already established. Second, biomarkers could improve the predictive value of imaging by distinguishing between progressive disease that is likely to be associated with events and stable disease that is likely to remain clinically silent. Biomarkers increase the sensitivity and specificity of risk prediction and increase the power to detect those individuals that need more aggressive primary prevention. Biomarkers directly involved in the pathogenic pathways leading to ASHD and its complications may serve as “titratable targets” for novel therapies against atherosclerosis, in a manner analogous to the way plasma LDL levels are currently used.

Since the last progress report, we have continued to make significant progress in our biomarker development program in several areas.

- 1) We have published 7 additional papers and submitted 4 others evaluating associations between individual biomarkers and ASHD or LVH phenotypes.
- 2) We have added 9 additional biomarkers through our collaboration with Biosite (San Diego, CA) and we have extended our contract with Biosite for an additional 3 years (**Table 3**).
- 3) We have established an agreement with Roche Diagnostics to measure high sensitivity troponin T (hs-cTnT). The study will leverage off our prior findings in DHS<sup>16</sup>. We think this biomarker has promise as a population screening tool to detect abnormalities in left ventricular structure and function.
- 4) Roche will also measure Growth Differentiating Factor-15 in the DHS this year.
- 5) We have developed data mining strategies to screen the enormous amount of biomarker data generated through our discovery programs.
- 6) We have made continued progress in the development of multiple biomarker panels for screening of ASHD and LV remodeling.

#### **Related findings this year:**

**Association between soluble receptor for advanced glycation end products (sRAGE) and atherosclerosis :** The receptor for advanced glycation end products (RAGE) is a transmembrane receptor expressed on a variety of cells. It modulates activity of several pro-thrombotic and pro-inflammatory mediators and has been implicated in the development and progression of atherosclerosis. A circulating isoform of RAGE, soluble RAGE (sRAGE), has been identified and theorized to competitively inhibit transmembrane RAGE-ligand binding thereby attenuating atherosclerosis, an hypothesis supported by the attenuation of atherosclerosis by administration of exogenous sRAGE in several animal studies. Few human data are available regarding the distribution of circulating sRAGE in the population and its association with atherosclerosis. Therefore, we measured plasma levels of sRAGE in the Dallas Heart Study and assessed its associations with coronary artery calcium (CAC).

**Results:** We observed an inverse, graded association between sRAGE quartiles and CAC, with CAC prevalence of 28.5% in quartile 1 compared with 15.7% in quartile 4 ( $p < 0.0001$ ). After multivariable adjustment, the associations between sRAGE levels in the 1<sup>st</sup> and 2<sup>nd</sup> quartiles (vs 4<sup>th</sup> quartile) and CAC remained statistically significant (adjusted OR 1.71, 95% CI 1.2 to 2.4; and 1.5, 95% CI 1.0 to 2.1, respectively).

**Interpretation:** In summary, we observed an independent and graded association between lower sRAGE levels and coronary atherosclerosis. With the data from prior basic science experiments and our hypothesis-generating observations, sRAGE appears to hold promise not only as a biomarker for atherosclerosis prediction, but also as a potential therapeutic target for the treatment and prevention of atherosclerosis and warrants further investigation.

**Table 3.** New biomarkers measured in the Dallas Heart Study (**Biomarkers measured since our last Progress Report are in bold type**).

<b>Biomarker</b>	<b>Description</b>	<b>Major findings and status</b>
<b>Adiponectin</b>	Adipokine: levels inversely related to insulin sensitivity	New assay run with HMW fragment
CCL11 (Eotaxin)	Eotaxin, eosinophil chemotactic protein	No association with ASHD phenotypes. Submitted to Atherosclerosis
sRAGE	Receptor for advanced glycosylation end products	Inverse association with CAC. Revision in review at Diabetes Care.
BNP 3-108	Unprocessed proBNP	Pending
LTBR	Lymphotoxin-beta receptor	Significant association with ASHD phenotypes. Paper in review at ATVB
CXCL2	Also known as macrophage inflammatory protein 2 $\alpha$	No association with ASHD phenotypes
CXCL1	Also known as neutrophil-activating protein 3	Modest association with ASHD. Submitted to Atherosclerosis
CCL 23 (MIP3)	Macrophage inflammatory protein 3; CCL23	Significant association with ASHD
Caspase 3	Caspase 3 is the executor molecule in apoptosis	Associated with atherosclerosis. Published in Apoptosis 2008
NGAL	Neutrophil gelatinase-associated lipocalin	Pending
PGLYRP-1	Peptidoglycan recognition protein	Associations with ASHD (Published in Atherosclerosis 2008)
sESAM	Endothelial cell-selective adhesion molecule	Significant (modest) association ASHD. Submitted to Circulation (with sICAM and sVCAM)
LP-PLA2	Lipoprotein Associated Phospholipase A2	Significant race/gender differences
Cystatin C	Marker of renal function	No association with ASHD Associated with LVH. In press at Circulation Heart Failure
<b>sICAM-1</b>	Soluble intercellular adhesion molecule-1	No independent association with ASHD
<b>sVCAM-1</b>	Soluble vascular cell adhesion molecule-1	No independent association with ASHD
<b>CT -1</b>	Cardiotrophin-1	No association
<b>MMP-9</b>	Matrix metalloproteinase -9	Associations with atherosclerosis and LVH
<b>MPO</b>	Myeloperoxidase	No independent association with ASHD. Modest association with LV remodeling
<b>PLGF</b>	Placental growth factor (angiogenic factor)	Modest association with ASHD
<b>IL-6</b>	Interleukin-6	No significant association with ASHD
<b>PAPP-A</b>	Pregnancy associated plasma protein-alpha	Associated with LVH

**Soluble endothelial cell-selective adhesion molecule (sESAM) levels are significantly associated with CAC and abdominal aortic wall thickness.** sESAM is a junctional adhesion molecule that is expressed in endothelial tight junctions and platelets and facilitates the transmigration of leukocytes across the endothelium<sup>17</sup>. Prior studies of soluble levels of cellular adhesion molecules (CAMs) and atherosclerosis have yielded mixed results<sup>18</sup>. We found significant associations between sESAM levels and CAC as well as abdominal aortic wall thickness, despite adjustments for other CAMs, including soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) (**Figure 13 and Table 4**). Interestingly, although sICAM-1 and sVCAM-1 were highly correlated with each other, sESAM was only weakly correlated with sICAM-1 and sVCAM-1, suggesting a distinct biological role from other CAMs.

Our epidemiologic findings of a link between sESAM and atherosclerosis are further supported by murine models of atherosclerosis in which ESAM gene deletion is associated with markedly reduced aortic atherosclerotic lesion size and reduced monocyte adhesion and endothelial migration. These findings were presented at the 2008 American Heart Association Scientific Sessions and stimulated interest from basic science investigators in further pursuing the mechanisms by which ESAM might play a role in atherosclerotic plaque development and progression.

**Table 4. sESAM, sICAM-1, and sVCAM-1 and Atherosclerosis Phenotypes**

	Models	sESAM		Log sICAM-1		Log sVCAM-1	
		OR [95%CI] <sup>†</sup>	p value	OR [95%CI] <sup>†</sup>	p value	OR [95%CI] <sup>†</sup>	p value
<b>CAC</b> <b>N=2468</b>	<b>Unadjusted</b>	1.5 [1.3-1.6]	<0.0001	1.1 [1.0-1.2]	0.055	1.1 [0.99-1.2]	0.09
	<b>Model 1*</b>	1.2 [1.1-1.3]	0.005	1.0 [0.9-1.1]	0.98	1.0 [0.9-1.1]	0.99
	<b>Model 2*</b>	1.2 [1.1-1.3]	0.005	0.98 [0.8-1.1]	0.79	0.98 [0.8-1.1]	0.77
	<b>Model 3*</b>	1.2 [1.1-1.3]	0.002	1.0 [0.9-1.2]	0.93	0.97 [0.8-1.1]	0.67
<b>AP</b> <b>N=2259</b>	<b>Unadjusted</b>	1.2 [1.1-1.3]	<0.0001	1.1 [1.0-1.2]	0.056	1.1 [0.99-1.2]	0.07
	<b>Model 1*</b>	1.1 [0.95-1.2]	0.34	1.0 [0.9-1.1]	0.95	1.0 [0.9-1.1]	0.77
	<b>Model 2*</b>	1.1 [0.96-1.2]	0.29	0.98 [0.9-1.1]	0.73	1.0 [0.9-1.2]	0.72
	<b>Model 3*</b>	1.1 [0.95-1.2]	0.29	1.0 [0.9-1.1]	0.96	1.0 [0.89-1.2]	0.85
<b>AWT</b> <b>N=2272</b>	<b>Unadjusted</b>	<b>Beta<sup>‡</sup></b>	<b>p value</b>	<b>Beta<sup>‡</sup></b>	<b>p value</b>	<b>Beta<sup>‡</sup></b>	<b>p value</b>
	<b>Unadjusted</b>	0.050	<0.001	0.02	0.000	0.02	0.001
	<b>Model 1*</b>	0.012	0.035	0.006	0.31	0.005	0.37
	<b>Model 2*</b>	0.013	0.039	0.005	0.56	0.000	0.99
<b>APB</b> <b>N=2257</b>	<b>Unadjusted</b>	0.225	<0.0001	0.087	0.04	0.075	0.08
	<b>Model 1*</b>	0.041	0.25	-0.019	0.60	-0.001	0.99
	<b>Model 2*</b>	0.049	0.18	-0.032	0.50	0.014	0.77
	<b>Model 3*</b>	0.053	0.163	-0.016	0.74	0.005	0.91

CAC=coronary artery calcium prevalence; AWT= abdominal aortic wall thickness; AP=abdominal aortic plaque prevalence; APB=abdominal aortic plaque burden

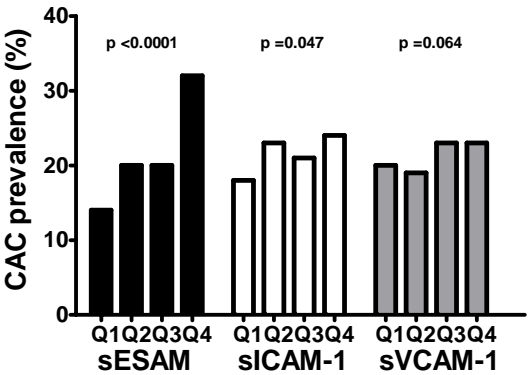
\* Model 1: adjusted for age, sex, race, hypertension, diabetes, current smoking, hypercholesterolemia, hypertriglyceridemia, low HDL-C, and BMI; Model 2: Model 1 plus sESAM, log sICAM-1 and log sVCAM-1; Model 3: Model 2 plus MCP-1

† Odds ratios reflect a change of one standard deviation (sESAM; 16.5 ng/mL) or one log unit (sICAM-1: 0.50 and sVCAM-1: 0.52)

‡ Beta estimates for AWT derived from linear regression and for APB derived from tobit linear regression per 1 SD increase in ESAM, log sICAM-1, and log sVCAM-1

**Multiple marker panels to improve prediction and detection of CHD.** The majority of subjects who have CHD events are misclassified as low or intermediate risk by the Framingham Risk Score (FRS). Very few new biomarkers (or genetic markers) improve CHD risk prediction, as CHD is complex and has many inciting factors. A single biomarker would reflect only a limited aspect of the processes promoting CHD. Only a few studies have looked at multiple markers together to improve risk prediction models; most have been very limited by their statistical design or study sample<sup>19 20-23</sup>.

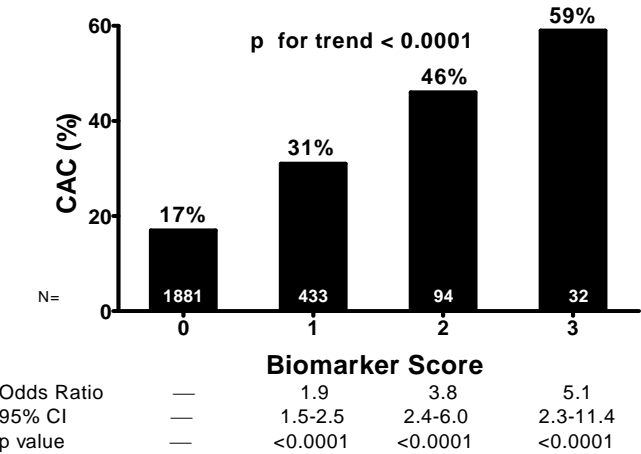
We have performed preliminary analyses to provide proof-in-concept that a multiple marker approach improves detection of atherosclerosis within the DHS. Utilizing 6 markers, including CRP, NT-proBNP, osteoprotegerin, sRAGE, PGLYRP-1, and sESAM, we constructed a biomarker score derived from the number of biomarkers  $\geq 95\%$  for sex and race. This biomarker score was significantly associated with increasing CAC and abdominal aortic wall thickness (Fig. 14). The biomarker



	Q1 (n=613)	Q2 (n=618)	Q3 (n=621)	Q4 (n=616)
sESAM	—	1.3 [0.9-1.9] p=0.13	1.1 [0.8-1.6] p=0.64	1.5 [1.0-2.1] p=0.03
sICAM-1	—	1.3 [0.9-1.8] p=0.10	1.2 [0.9-1.7] p=0.22	1.1 [0.8-1.6] p=0.46
sVCAM-1	—	0.9 [0.6-1.2] p=0.49	1.0 [0.7-1.4] p=0.93	1.0 [0.7-1.4] p=0.83

Odds ratios with 95% confidence intervals for CAC score > 10 compared to Quartile 1 adjusted for age, sex, race, hypertension, diabetes, current smoking, hypertriglyceridemia, low HDL-C, and BMI

**Figure 13.** Increasing quartiles of sESAM, but not sICAM-1 or sVCAM-1 are associated with CAC prevalence.



\* Odds ratios adjusted for Framingham risk categories

**Figure 14:** Biomarker score was significantly associated with increasing CAC (left) and increasing abdominal aortic wall thickness (right).

score also improved the c-index, or the ability to discriminate between those with and without coronary calcium as well as improved reclassification into higher and lower risk categories compared to the FRS alone (**Table 5**). These preliminary findings support the concept that multiple marker strategies optimized to maximize specificity can improve the ability to detect atherosclerosis.

**Table 5.** Biomarker Score Improves Prediction of CAC beyond Framingham Risk Score (FRS)

	c statistic	Likelihood $\chi^2$	BIC	AIC	NRI	IDI
<b>FRS</b>	0.71*	373	2232	2180	—	—
<b>FRS + Biomarker Score</b>	0.75*	414	2195	2145	14.2%*	2.4%*

BIC = Bayesian Information Criterion (lower value indicates better model selection)

NRI = Net Reclassification Index

AIC = Akaike Information Criterion (lower value indicates better model selection)

IDI = Integrated Discrimination Index

p < 0.0001 for comparisons between models

Over 35 analytes have been measured in the DHS that are potential candidates for inclusion in a multiple marker panel (**Table 6**) and an additional 12 markers will be available within the next 6 months.

**Table 6. Novel markers measured in the Dallas Heart Study**

hs C-reactive protein	Troponin-T	Fructosamine
Monocyte chemoattractant protein-1	Brain Natriuretic Peptide	Soluble endothelial cell-selective adhesion molecule
Soluble CD40 ligand	NT-proBNP	CXCL1
Interleukin-6	BNP 3-108	CXCL2
Interleukin-18	Soluble receptor advanced	CCL 23 (MIP3)
Lipoprotein phospholipase-2	Cystatin C	CCL11-Eotaxin
Lipoprotein (a)	Soluble ICAM-1	Lymphotoxin Beta receptor
Osteoprotegerin	Soluble VCAM-1	Caspase-3
Adiponectin	Uric acid	Neutrophil Gelatinase-Associated Lipocalin (NGAL)
Leptin	Urine microalbumin	Peptidoglycan recognition protein-1
Matrix metalloproteinase-9	Cardiotrophin-1	Placental Growth Factor (PLGF)
Myeloperoxidase	Pregnancy associated plasma protein alpha	FSH
Beta Crosslaps	Lipoprotein subfractions (NMR)	LH
Insulin	Anti- Ox LDL (E06)	Testosterone
ANA	Chem 20	Sex Hormone Binding Globulin

#### Goals:

- Complete assays and analyses of hs-cTnT and GDF-15 from DHS-1

- Develop mature multiple-biomarker panels for detection of prevalent atherosclerosis, LVH, and LV systolic dysfunction
- Continue to add new biomarkers to the DHS portfolio through our collaborations.
- Correlate baseline biomarker data and biomarker panels with new phenotypes generated via DHS-2, including
  - Development and progression of ASHD
  - Left ventricular structural remodeling
  - Carotid plaque morphology
  - Cognitive function and structural brain abnormalities
- Negotiate contracts with Biosite and Roche for measurement of analytes from DHS-2

***Future directions and translation to clinical practice:*** Biomarkers that are associated with ASHD will be incorporated into a risk prediction algorithm. These biomarkers would also have clinical utility as low-cost screening tools for ASHD, and may serve as a “gatekeeper” for more expensive imaging modalities. Given the high costs of drug development, and the absence of suitable low-cost surrogate markers of atherosclerosis, marker(s) that accurately characterize ASHD development and progression would have tremendous value in drug development, both in identifying targets and monitoring novel therapies.

### **III. Key Research Accomplishments**

- Philips Achieva 3.0T MRI System was accepted for clinical use on September 28, 2007.
- Installation of an 8-channel surface coil for improved carotid imaging
- Upgrade of the 3.0T MRI system to 32 receiver channels to support the use of larger arrays of coils and multiple coils for more rapid imaging
- Installation of a 32 channel cardiac coil to investigate the potential for more rapid cardiac imaging using SENSE and kt-SENSE techniques
- Implementation of a focal shimming technique to reduce image artifacts due to magnetic susceptibility differences.
- A total of 1865 DHS-2 participants have undergone imaging using the 3.0T MRI.
- A total of 3099 participants (all groups) have been enrolled in the Dallas Heart Study-2.
- Assessment of ventricular volumes and function: The use of 3T MRI permits more rapid assessment of ventricular function through the use of parallel imaging (SENSE). This allows us to obtain additional measures of ventricular and atrial function.
- Tagging studies of cardiac function: Myocardial tagging has been performed to evaluate left ventricular systolic and diastolic function in each participant. Harmonic phase (HARP) analysis has been implemented to measure regional myocardial strain and rotation. A data analysis pipeline has been developed to address the effects of tag fading during the cardiac cycle to insure the quality of the data for the assessment of diastolic function.
- Brain MRI to assess Brain Volume: Analysis of brain volumes has been completed in 1800 participants and demonstrates the expected distribution of brain volume and grey matter volume with means and standard deviations consistent with ranges reported in the literature. In addition automated techniques have been implemented to perform regional brain segmentation. This segmentation has been performed in 921 participants and the results are undergoing initial review.
- Brain MRI for white matter hyperintensities: We have developed and implemented an automated method for the detection of white matter hyperintensities on FLAIR images of the brain. The new

automated method has been presented at a national meeting and a manuscript is in preparation. It has been used to quantify white matter hyperintensities in 1800 DHS-2 participants

- Establishment of new abdominal aortic atherosclerosis phenotypes, including quantitative measures of aortic plaque. Initial analysis of the abdominal aorta has been performed in 1260 participants.
- Developed a new measure of atherosclerosis: abdominal aortic wall thickness.
- Implemented imaging and analysis protocols for the assessment of carotid wall thickness and the characterization of carotid plaque.

#### **IV. Reportable Outcomes- Manuscripts, abstracts, presentations, funding applied for, employment, research opportunities**

- Maroules CD, McColl R, Khera A, and Peshock RM. Interstudy Reproducibility of SSFP Cine Magnetic Resonance: Impact of Magnetic Field Strength and Parallel Imaging. *Journal of Magnetic Resonance Imaging*, 2008; 27:1139-1145.
- Maroules CD, McColl R, Khera A, and Peshock RM. Assessment and Reproducibility of Aortic Atherosclerosis MR Imaging: Impact of 3-Tesla Field Strength and Parallel Imaging. *Investigative Radiology*; 2008;43:656-662.
- Invited presentation: American College of Cardiology, 2008: Detection of Subclinical Disease: Major Trials using Cardiovascular Magnetic Resonance: Dallas Heart Study.
- Invited presentation: International Society for Magnetic Resonance in Medicine, 2008 Cardiac MRI: Emerging Applications and Challenges—Cardiac MRI at 3T or Higher.
- Poster presentation: Hulsey K, et al. Automated quantification of white matter hyperintensity burden using MPRAGE and FLAIR Images. *International Society for Magnetic Resonance in Medicine* 2009.
- Rosero EB, Peshock RM, Khera A, Clagett P, Lo H, Timaran C. Agreement between Methods of Measurement of Mean Aortic Wall Thickness by Magnetic Resonance Imaging. *Journal of Magnetic Resonance Imaging* 2009;29:576-582

#### **V. Conclusion**

The results up to this point indicate that 3T MRI permits rapid and extensive evaluation of the heart, systemic atherosclerosis and end-organ damage in the brain. These imaging approaches are widely available in the clinical arena and the results of the Dallas Heart Study can be directly applied in the care of patients.

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